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REVIEW

A Systematic Review and Meta-analysis of Endovascular Repair (EVAR) for Ruptured Abdominal Aortic Aneurysm

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Abstract *Background:* Endovascular abdominal aortic aneurysm (EVAR) repair has become a well-established technique in the treatment of elective abdominal aortic aneurysms (AAAs) due to proven benefits in mortality, hospital stay and operation time compared to open repair. The aim of this study was to estimate the mortality rate from EVAR due to ruptured abdominal aortic aneurysm (RAAA).
Methods and materials: A systematic review and meta-analysis of all English language literature with information on mortality rates from EVAR for RAAA was conducted.
Results: The pooled mortality rate from RAAA after EVAR across 31 studies concerning 982 patients was 24% (95% confidence interval (CI) 20—28%). The pooled morbidity from 21 studies was 44% (95% CI 33—55%). The average procedure time was 155.1 min, with an intra-operative blood loss of 523 ml and hospital stay of 10.1 days. There is evidence of publication bias suggesting the mortality rate may be under-estimated.
Conclusions: Mortality from EVAR for RAAA appears to be lower than that which is reported for open repair of RAAA. However, the high level of publication bias cannot be ignored and may actually indicate higher mortality rates.

Introduction

Abdominal aortic aneurysm (AAA) represents a significant problem due to the risk of rupture. Death rates from ruptured abdominal aortic aneurysm (RAAA) in the UK reached 4073 in 2005 affecting more than twice as many

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men than women.[1] Although much has changed over the years regarding the overall management of these patients, very little had altered concerning the operative methodology until 1991.[2] Prior to this, Creech's method of open repair for AAA was the only curative option, but required high risk surgery.[3] However, since the introduction of endovascular repair (EVAR) by Parodi et al.[2], less invasive methods can be adopted.

Several large trials have shown multiple benefits with EVAR compared to open surgery in elective repair of AAA.[4–6] A three-fold reduction in mortality coupled with a shorter length of hospital stay and operation time has increased the popularity of EVAR. This has led to many questioning whether these benefits can also be achieved in the emergency setting.

The aim of this study was to determine the mortality rate from EVAR for RAAA by performing a systematic review and meta-analysis of the relevant literature.

Methods

Search strategy

The primary author (H.S.R.) performed a literature search of the Medline (1950–2007) and Embase (1980–2007) databases using the Ovid search engine (version 10.5.6; Ovid Technologies Inc., New York, USA). The following search strategies were used on each database:

'Aortic aneurysm, abdominal ***and*** *exp* rupture (textword) ***and*** *exp* endovascular' (textword)
'Aortic aneurysm, abdominal ***and*** *exp* rupture (textword) ***and*** *exp* stent' (textword)

The search was restricted to articles published in English and to studies in humans. Where possible, abstracts were reviewed online and suitable articles downloaded for data extraction. If abstracts were not available, a full copy of the article was assessed. All articles were obtained electronically or via the University of Leicester or British libraries. For completeness, the reference lists from retrieved articles were searched manually as was the reference list of several book chapters previously written by some of the co-authors.

Study selection

The main criterion that was sought for inclusion into the study was the availability of data on mortality rates after emergency EVAR for ruptured AAA. Articles were not restricted due to design of study (retrospective, prospective, observational, etc.), operative techniques, or stent-graft design. Articles that gave details of acute AAA as opposed to ruptured AAA were excluded as acute AAA often meant symptomatic but non-ruptured AAA. The accepted definition of ruptured AAA was blood/haemorrhage outside the aneurysm wall on CT. Any article that did not define this was excluded. Case reports, review articles, letters, editorials, series of less than 5 patients and articles that focused on one group of patients (e.g. octogenarians) were also excluded. Figures for reported elective cases alongside ruptured cases were ignored. Where multiple publications relating to the same centre were identified, the most comprehensive article was analysed and the others excluded as a protective measure against counting data multiple times in the analysis.

Data extraction

All articles were reviewed by the corresponding author (H.S.R.), who in conjunction with the other authors (M.J.B. and A.J.S.) performed the analysis. In addition to study demographics (dates of study, length, type and location, etc.), mortality and morbidity outcomes for patients undergoing emergency EVAR for ruptured AAA were recorded for each study. Data was extracted as the total number of patients experiencing each event; where percentages were given, the numerator figures were derived using these percentages and the total number of patients. Mortality rates were taken as in-hospital or 30-day mortalities. Difficulties arose when recording morbidity data as studies used individual classification criteria. Due to this, all morbidity ranging from mild (wound infections) to severe (organ failure) was grouped together. Length of hospital stay and amount of blood loss were also extracted if quoted in an individual article. Different measures of central location were reported in different papers (i.e. mean, median or mode) but for the purposes of analysis, these differences in definition were ignored. The mid-date of the study (i.e. the date calculated to represent the halfway point through the study time period) was also extracted as a potential covariate in the meta-analysis.

Quantitative data synthesis

Meta-analysis is a statistical tool used to combine results of independent studies to obtain a more precise estimate of outcomes and to explore differences between study results.[7] Before such analysis can be performed, heterogeneity between studies which statistically tests the degree of similarity between study outcomes is usually determined.[8]

If the heterogeneity is low then 'fixed-effects model' analysis should be used for data analysis, but if the heterogeneity is high, the 'random-effects model' is used. The 'random-effects model' is a statistical model in which both intra-study error and inter-study variation are accounted for in the assessment of uncertainty.[7]

Separate meta-analyses were performed for operative mortality and morbidity. Both were performed using random-effects models on a log odds outcome scale (i.e. a log(proportion/(1 − proportion)) transformation). The log odds scale is used because, unlike the probability scale, it is not bounded and, thus, has more desirable statistical properties.[7] We quantify the proportion of the between study variability beyond that which we would expect purely by chance using the I^2 statistic[9] and the random effect included in the model allows for any such heterogeneity (in addition to chance variation) between study results.[7]

In an attempt to explain between study variability, the covariates' mid-date of study and an indicator for Europe or USA setting were included in the meta-analysis model, extending it into a meta-regression model.[10] This was done to explore whether mortality and morbidity had changed systematically over time. Publication bias was assessed using funnel plots, and using Egger's test.[11]

Although we intended to conduct meta-analyses for average hospital stay and intra-operative blood loss, this proved not to be possible due to measures of precision associated with these quantities not being reported in the primary papers. Instead, simple un-weighted averages are reported (with no indication of uncertainty).

Results

In total, 813 articles were identified using the search strategies mentioned above (Fig. 1). 787 were identified from computerised searches and 26 additional articles via manual searches of reference lists. 741 abstracts were rejected for the reasons listed in Table 1, leaving 72 articles for closer scrutiny.

Of these remaining 72 articles, 21 were duplicate entries or old series of data reported in later publications, leaving 51. Paper copies of these 51 articles were obtained for further assessment. Twenty further articles were excluded at this stage due to the reasons given in Table 2, leaving 31 which met our inclusion criteria for the meta-analysis.

Study characteristics

There were 9473 patients presenting with an acute AAA and 1056 emergency EVARs were performed (11%). Thirty-one articles were included in the analysis and reported 982 patients who underwent EVAR for RAAA[12–42] (Table 3).

All studies quoted mortality figures but only 21 (68%) gave morbidity data.[12,14–16,18–21,23,25–28,32–35,37,40–42] European studies accounted for almost two-thirds (71%, 22 out of 31 studies) and USA data for approximately one-third (29%, 9 out of 31 studies). There were no studies outside Europe or the USA. Of the patients undergoing emergency EVAR, 86% were men (based on data reported in 25 studies). The average age for the open repair group for RAAA from the 14 studies which reported it was 72.4 years. Five studies commented on the average age in the EVAR group, which was 74.1 years. Twenty studies reported the average size of the AAA preoperatively using either mean or median statistics. The arithmetic mean of these statistics gave an average preoperative AAA size of 7.28 cm.

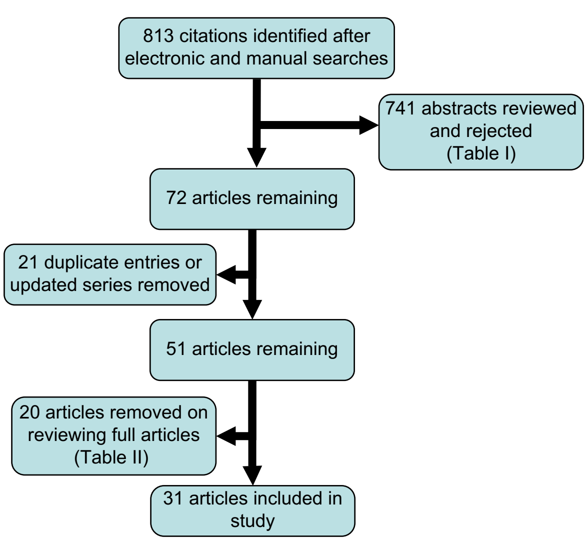

Figure 1 Flowchart of systematic review.

Table 1 Reasons for rejection of articles from online abstract

Case reports, review articles, articles with cohort less than five patients
Specific age groups (e.g. octogenarians)
No mortality data
Thoracic EVAR
No EVAR offered
Elective repairs only
RAAA not defined
Not in English language

Meta-analysis

The overall pooled estimate for mortality rate of ruptured AAA after treatment with EVAR from all 31 studies was 24% (95% CI 20–28%). Results of this meta-analysis are displayed as a forest plot (Fig. 2). In this plot, the point estimate (represented by a black dot) and the 95% CI (represented by a horizontal line) for the proportion of people who die are plotted for each study. The point estimate and 95% CI, reported on the proportion scale, are also provided in the far-most right-hand column of the plot. The point estimate (black dot) is surrounded by a grey box whose area represents the weight of the study in the overall meta-analysis. The relative weight given to each study is provided to the right of the plot as a percentage. The pooled estimate for the meta-analysis is presented directly below the estimates from the 31 studies and is represented as a 'diamond' with the centre corresponding to the point estimate and the extreme tips spanning the 95% CI. There was statistically significant heterogeneity between study results on the log odds scale ($\chi^2 = 58.73$; d.f. $= 30$; $P = 0.001$) resulting in an I^2 value of 49% indicating moderate heterogeneity between studies.

The overall pooled estimate from 21 studies for morbidity post-EVAR (in those who survive) for RAAA was 44% (95% CI 33–55%) (Fig. 3). Again heterogeneity between studies on the log odds scale ($\chi^2 = 81.23$; d.f. $= 20$; $P < 0.001$) was statistically significant resulting in an I^2 value of 75% indicating a high degree of heterogeneity between studies.

Table 2 Reason and frequency of rejection of articles from paper copies of article

Reason for rejection	Number
Review articles	8
Elective cases only	5
No mortality data	3
No EVAR offered	2
Thoracic aneurysms	1
Non-English	1

Table 3 Studies included in the systematic review and meta-analysis

Author	Published date	Place of origin	Start date	End date	Average AAA size	n	Mortality	Morbidity
Oranen[12]	2006	Euro	May-98	Aug-05	7.4[a]	34	6	7
Kampa[13]	2005	Euro	Jan-98	Aug-04		25	5	
Peppelenbosch[14]	2003	Euro	May-01	Jun-02	6.7	16	4	8
Vaddineni[15]	2005	USA	Oct-99	Jul-04	6.7	9	2	4
Hechelhammer[16]	2005	Euro	Jun-97	Jul-03	7.7	37	4	7
Rubin[17]	2004	USA	Jun-00	May-01	8.3	5	1	4
Coppi[18]	2006	Euro	Dec-99	Apr-06	7[a]	33	10	9
Greco[19]	2006	USA	Jan-00	Jan-03		290	114	32
Alsac[20]	2005	Euro	Jan-01	Jul-04	8.5[a]	17	4	9
Castelli[21]	2005	Euro	Jan-01	Jan-04	7.3	25	5	7
Leon[22]	2005	USA	Jan-95	Dec-03		54	20	
Lombardi[23]	2004	USA	Jun-01	Jul-03	6.5	5	0	2
Acosta[24]	2006	Euro	Jan-00	Dec-04		56	19	
Reichart[25]	2003	Euro	Oct-00	Apr-02	6.4	6	1	2
Peppelenbosch[26]	2006	Euro/Canada	Feb-03	Sep-04	7.5	49	17	20
Peppelenbosch[27]	2005	Euro	May-01	Feb-04		35	8	10
Ohki[28]	2000	USA	Apr-94	Apr-00	7.25[a]	20	2	8
Franks[29]	2006	Euro	Jul-96	Apr-03		10	1	9
Brandt[30]	2005	Euro	Jan-01	Sep-04	7.1	11	0	
Mehta[31]	2005	USA	Jan-02	Dec-04		23	7	
Hinchliffe[32]	2001	Euro	Jan-94	Jan-00		19	9	7
Gerassimidis[33]	2005	Euro	Mar-98	Oct-04	7.8[a]	23	9	13
Lee[34]	2004	USA	Jan-97	Mar-04	7.6[a]	13	1	8
Scharrer-Pamler[35]	2003	Euro	Jan-95	Jan-01	7.2	24	5	11
Resch[36]	2003	Euro	Jan-97	Jul-02	7	21	4	
Lagana[37]	2006	Euro	Jul-01	Oct-04	7.1	30	3	7
Lachat[38]	2002	Euro	Aug-98	Sep-01	7.1[a]	21	2	
Yilmaz[39]	2002	Euro	May-99	Dec-01		17	4	
Veith[40]	2002	USA	Jan-94	Jan-02		25	3	4
Larzon[41]	2005	Euro	May-01	Jan-04		15	2	9
Arya[42]	2004	Euro	Jan-99	Jan-03	7.5	14	2	1

[a] Median values. All others are mean.

Un-weighted average procedure time from the 20 studies that reported this outcome was 155.1 min. The longest procedure time[28] (336 min) was from one of the three oldest studies that began in 1994,[28,32,40] and the shortest operative time was 80 min from a study performed between 2001 and 2004.[37]

Intra-operative blood loss was reported in 14 studies and the un-weighted average was 523 ml. Although, not surprisingly, the largest blood loss (1200 ml) was from one the oldest studies in the group,[32] a more recent study ending in 2002 had the second largest recorded losses of 1100 ml.[14] The smallest loss was recorded at 138 ml and was from a study ending in 2004.[34]

Although 21 studies looked at total hospital length of stay, only six studies recorded Intensive Care Unit (ICU) stay (un-weighted average 113 h). The shortest and longest stays were from 2 different studies completed in 2004, and were 5 days[13] and 19.5 days,[15] respectively. The combined average was 10.1 days.

Meta-regression

Meta-regression analysis aims to relate the size of effect to one or more characteristics of the studies involved.[43] To investigate whether mortality and morbidity systematically varied over time, mid-point of the study was included as a covariate. There was little suggestion of such a relationship with the analyses producing P-values of 0.667 and 0.926 for mortality and morbidity, respectively. Therefore, there is little evidence to suggest a significant change in morbidity or mortality over time in this data set. The mortality and morbidity data was further analysed to see if there was any difference if the study was from Europe or the USA. Again this analysis was not statistically significant ($P = 0.374$ and 0.490, respectively).

Mid-point was also included in an un-weighted regression for blood loss, intra-operative time and length of hospital stay. The duration of the procedure compared to mid-point of study does seem to have a positive relationship with a lower intra-operative time for the more recent studies (20 studies; $P = 0.024$), implying that the intra-operative time for EVAR is reducing with more experience. There was no significant association when comparing average blood loss (13 studies; $P = 0.132$), hospital stay (21 studies; $P = 0.235$) or ITU stay (6 studies; $P = 0.202$) with the mid-point of study. Therefore, although average procedure time seems to be less since 1994, there is no significant improvement in average blood loss, hospital and ITU stay.

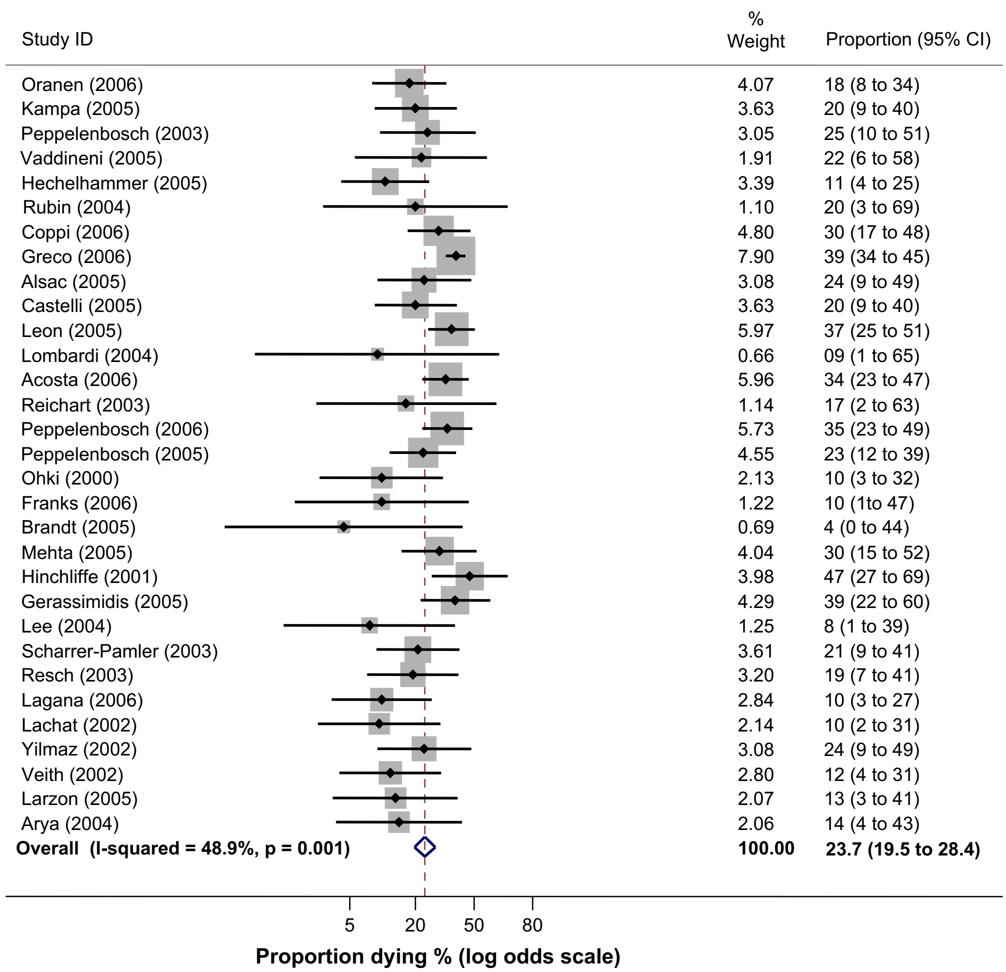

Figure 2 Forest plot of studies reporting mortality figures.

Assessment of publication bias

'Publication bias occurs when the publication of research results depends on their nature and direction'.[44] Bias is usually due to authors only publishing or editors only accepting research that shows positive significant results, with all research that shows inconclusive or negative results being excluded from publication.

Funnel plots were used for mortality and morbidity outcomes to assess whether publication bias occurred in this meta-analysis.[45] In essence, these are scatterplots of outcome against a measure of study size (e.g. standard error of the outcome in Figs. 4 and 5). Since larger studies should measure outcomes more precisely because random error is diminished, in the absence of publication bias the plot should appear symmetrical about the pooled estimate with increased variability between study estimates the larger the standard error – producing a funnel shape. If studies are systematically suppressed (i.e. negative results remain unpublished) then this can be identified by "gaps" in the funnel making the plot asymmetric.

In the funnel plot for mortality (Fig. 4) ($n = 31$ studies) there was a large degree of asymmetry with a suggestion that studies corresponding to high rates of mortality are missing on the right-hand side of the plot especially in the lower right corner of the plot. A formal regression test for publication bias (which tests how a best line fit through the funnel deviates from a vertical line – included in Fig. 4) supports this visual interpretation ($P < 0.001$). The most likely cause for this asymmetry is publication bias but other interpretations should not be ruled out.[46] We did not screen the results before the analysis stage and therefore could not have removed these articles. The most likely cause is that smaller studies with negative results are not published.

The funnel for morbidity is also irregular (Fig. 5) ($n = 21$ studies) but it is less easy to discern where exactly studies are missing and thus speculate the cause for this distribution of outcome estimates. The test for asymmetry results in a P-value of 0.006.

Discussion

The results of this study demonstrate an operative mortality rate of 24% after treatment with EVAR for RAAA and a morbidity rate of 44%. Other outcome measures are much more difficult to comment on due to the lack of comprehensive data. However, the average operative time was estimated at just over 2.5 h with an estimate of average blood loss just over half a litre. The average total

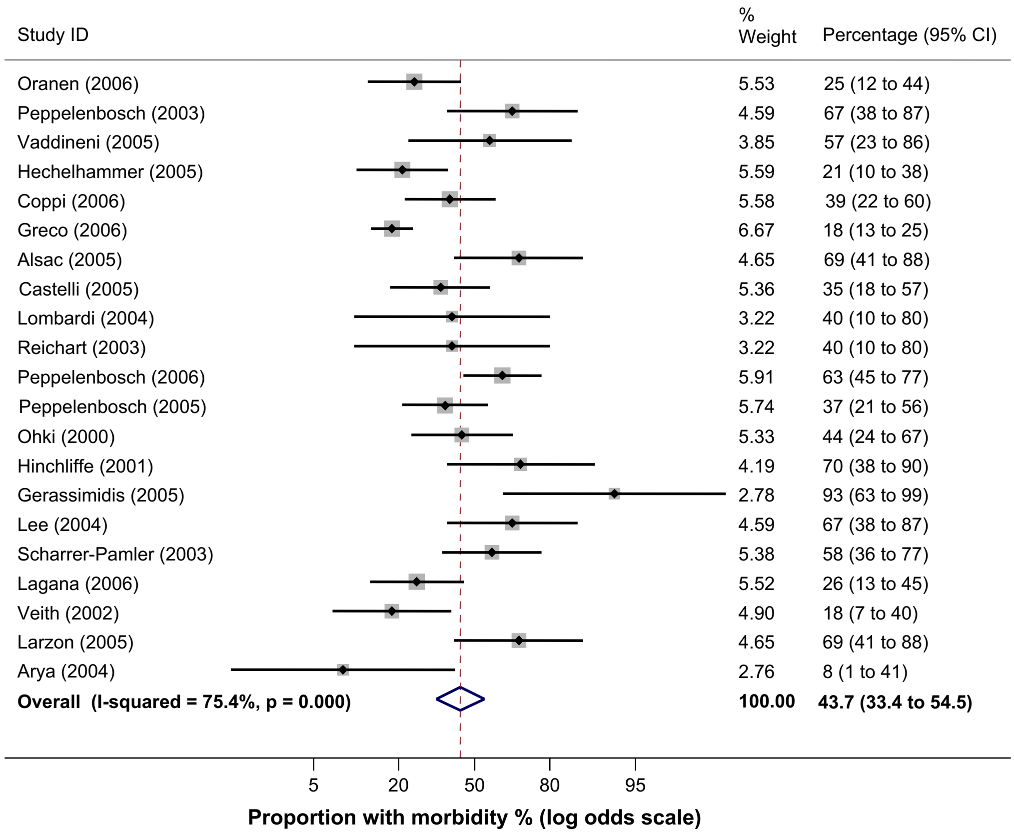

Figure 3 Forest plot of studies reporting morbidity data.

hospital stay after EVAR for RAAA was 10.1 days in the studies which report it.

Our results compare favourably with recent research that attempts to obtain definitive answers about the successes and failures of EVAR in the emergency setting. Visser et al.[47] conducted a systematic review of 10 studies comparing EVAR to open repair in RAAA and quoted a mortality rate of 22% in EVAR for RAAA, with a 28% rate of systemic complications. In the same year, Harkin et al.[48] conducted a similar study but included 34 studies and quoted an even lower rate of mortality (17%). Similar rates of mortality were found by Mastracci et al.[49] (21%) during a systematic review on the same topic consisting of 18 studies. However, although these results are encouraging, results from a recent small randomised control trial are much different. Hinchliffe et al. report on 32 patients and quote similar mortality and post-operative complication rates between open and endovascular repair of RAAA (53% mortality in both groups; 77% complications for EVAR and 80% complications for open).[50]

Death rates from open RAAA repair are high and little has changed in recent years. Bown et al. showed a gradual

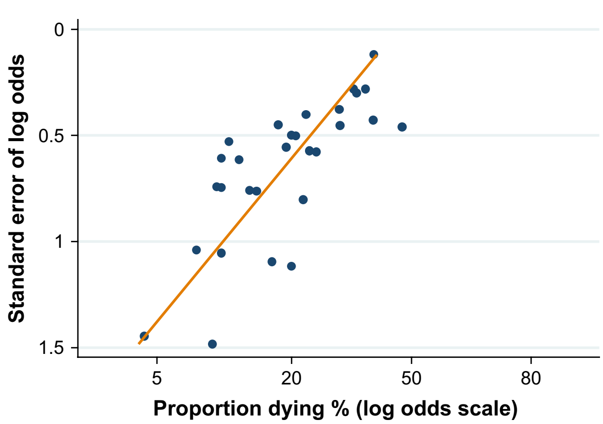

Figure 4 Funnel plot to assess publication bias from mortality data. This shows a large gap in the lower right-hand side of the plot indicating publication bias.

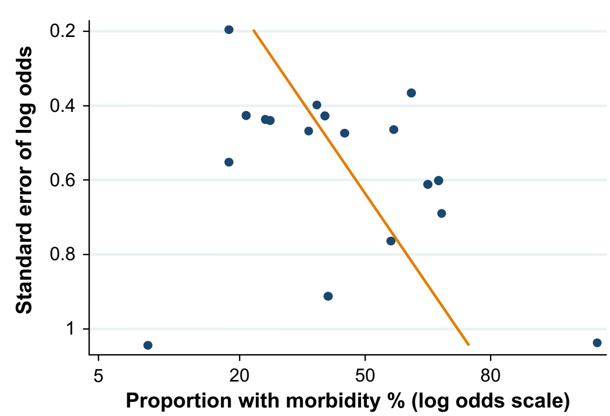

Figure 5 Funnel plot to assess publication bias from morbidity data.

reduction in operative mortality over time (approximately 3.5% per decade) with estimated operative mortality rate from open repair for RAAA in 2000 at 41%. This figure remains high despite advances in intensive care medicine and the development of specialist vascular centres with separate on-call services. This study also concluded that this constant improvement in survival would not be continued but instead would level off at a maximum beneficial level.[51] The major contributing factors to mortality following open repair of RAAA are multiple organ failure (MOF) and shock.[52,53] Both, in theory, can be minimised by using endovascular methods of repair. The operation can also be performed quicker, under local anaesthetic and with less blood loss to improve chances of survival.

However, the main obstacles preventing global usage of this technique are logistical.[32] Establishing an on-call EVAR service would require formulation of a dedicated multidisciplinary team involving surgeons, anaesthetist, and staff from the wards, theatres and from the Radiology Department. Radiology services must be made available and appropriate equipment (e.g. stent grafts, imaging devices) must be readily available.

Without formal EVAR programmes for RAAA in place, no higher level evidence is obtainable, leaving us to draw conclusions from retrospective studies alone. If emergency EVAR protocols are to be established then certain issues need to be addressed. Funding and the services of hospital departments and equipment are major problems.

Previous studies have shown an increased cost of open repair of RAAA as compared to elective open repair; some even as high as five times more per life saved per year.[54] The costs from emergency repair of RAAA via EVAR are likely to be even higher. Other trials have also highlighted the need for lifetime follow-up and the costs incurred from this.[55] There are obviously mixed views regarding the cost-effectiveness, but after initial expense to establish an EVAR protocol, the costs are likely to decrease. Whether these costs are acceptable is yet to be determined.

One possible solution to help reduce costs could be adopted during the follow-up period. Several papers have highlighted the acceptability of using duplex ultrasound scanning (DUSS) in the post-operative period rather than computed tomography (CT) to assess the success of the repair and the need for any secondary interventions.[56–58] Not only is DUSS much cheaper than CT, but also safer.

Using EVAR for RAAA is the next challenge for vascular surgery. However, whilst elective EVAR has been welcomed due to evidence-based data showing its worth; no such data exists for RAAA. The best possible way to determine whether EVAR for RAAA is a worthwhile venture would be to conduct a randomised controlled trial. However, even though all the logistical issues discussed above can be overcome, there is still a major hurdle to performing this type of definitive study. Obtaining informed consent from moribund patients to allow them to be randomised into such a trial raises several ethical and legal issues. Therefore, the best evidence available on EVAR for RAAA may be determined from meta-analyses of non-randomised studies.

Whilst several meta-analyses have been conducted, our paper aims not only to show the results of our outcome measures but also to highlight the problem with publication bias through detailed and correct statistical methods. We have been able to demonstrate that whilst the results of our meta-analyses are encouraging for the use of EVAR in the emergency setting, the results need to be interpreted with caution due to the lack of complete data in the published literature. Using statistical analysis we have shown that the lack of large randomised controlled trials and smaller published studies may lead to inaccurate results. We have also appreciated bias and specifically determined the extent of this.

There are several limitations of the study. Meta-analyses can only be as accurate as the studies used and therefore introduce an element of error. All relevant articles were searched as described and although every effort was made to retrieve all the articles on this subject, undoubtedly, some may have been missed. Although we feel there are no duplicate data sets, this was difficult to confirm, especially when considering studies from the same centre at different time points. To overcome this, the most comprehensive relevant study was included after a review of all the studies.

Problems with non-uniform classification categories, for example with morbidity, were also highlighted by the study. For several reasons, in this study we have grouped all morbidity, ranging from mild to severe, together. All papers use their own classification methods for assessing morbidity. Whereas some classify morbidity as mild, moderate, and severe, with no explanation of group entry criteria, others classify them systemically. To prevent problems in data analysis we decided to group all morbidity together. Any complication from surgery, even as minor as a wound infection, may require hospital referral and would therefore impact on the success of EVAR, and have implications on its use for RAAA.

Studies in languages other than English were not included and may have been relevant to the data set. In an attempt to obtain all the relevant literature a manual search was performed as well as electronic searches. There are only 31 studies included in this meta-analysis, and whilst we acknowledge that this is a relatively small number, it is the entire published literature on this subject.

Conclusion

This study demonstrates mortality and morbidity from EVAR for RAAA of 24% and 44%, respectively. EVAR for RAAA whilst initially being expensive (mainly due to the cost of the grafts) is associated with lower rates of hospital stay (including intensive care stay) and higher rates of independence post-operatively, which would reduce total costs. These points coupled with a lower mortality rate provide a healthy discussion regarding the future for EVAR in cases of RAAA.

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